In the Specification (clean copy as amended)

Please replace the paragraph bridging pages 11 and 12 with the following:

A chimeric protein consisting of the α chain of an integrin and the heavy chain or light chain of an immunoglobulin refers to a molecule in which the extracellular region of the α chain of an integrin is bound to the constant region of the heavy chain or light chain contained in an immunoglobulin. In this case, a chimeric protein in which the N terminus side of the protein is an integrin molecule and then connected to an immunoglobulin molecule side by side is preferable. A chimeric protein consisting of the β chain of an integrin and the heavy chain or light chain of an immunoglobulin refers to a molecule in which the extracellular region of the β chain of an integrin is bound to the constant region of the heavy chain or light chain contained in an immunoglobulin. Also in this case, a chimeric protein in which N terminus side of the protein is an integrin molecule and then connected to an immunoglobulin side by side is preferable. In either case of α chain or β chain, a chimeric protein bound to the heavy chain of an immunoglobulin is preferable.

Please replace the paragraph bridging pages 13 and 14 with the following:

A DNA coding for the α chain and β chain of an integrin can be obtained using the information of known cDNA sequences by such a method as gene amplification based on the PCR method, cDNA cloning or DNA synthesis. For example, the DNA sequences of α4 and β1 are already reported in literature (Takada, Y. et al., EMBO J., 8, 1361-1368 (1989), Scott Argraves, W. et al., J. Cell Biol., 105,

1183-1190 (1987)). A DNA coding for the α chain and β chain of an integrin can also be obtained by expression cloning using an antibody, etc. For binding to a DNA coding for the constant region of an immunoglobulin, it is desirable to take out a DNA coding for the extracellular portions only of the α chain and β chain of an integrin. For this purpose, it is preferable to use the PCR method and DNA synthesis. The extracellular portion of either an α chain or β chain refers to the polypeptide sequence on the N terminus side from the portion speculated to be the transmembrane portion. Its partial sequence can also be used as far as the ligand binding capability is retained, but it is preferable to use most of the portion considered to be an extracellular region. For taking out a DNA, it is necessary to adjust for adaptation of frames after linking to a DNA coding for an immunoglobulin. For example, this can be achieved by modifying the primer when a DNA fragment is taken out by the PCR method. In this case, it is desirable to design for ensuring that amino acid modification is not caused by the base substitution of the primer. However, amino acid substitution is allowed if the function of the chimeric protein is not changed. For obtaining a DNA by chemical synthesis, the purpose can be achieved by designing a sequence to ensure the linking to a DNA coding for an immunoglobulin. In the case of cDNA, a DNA capable of being bound to a DNA coding for an immunoglobulin can be prepared by using DNA fragmentation and a synthetic DNA.

Please replace the paragraph bridging pages 16 and 17 with the following:

If the obtained recombinant vector is transfected into a cell, a cell capable of producing an integrin-immunoglobulin chimeric protein heterodimer complex can be obtained. In this case it is preferable to use an animal derived cell as a host. For example, a COS cell (simian renal cell), CHO cell (Chinese Hamster ovarian cell), Sf9 (insect cell), etc. are generally used as hosts. Furthermore, myeloma cells such as P3UI and Y3 can also be used. Other established cell lines and cloned cells can also be used, but the cells used as hosts are not limited to them. In the present invention, it is preferable to use a CHO cell.

Please replace the paragraph bridging pages 18 and 19 with the following:

In any transfection method and any combination of vectors, it is important to select a cell which is transfected by the two recombinant vectors and produces a chimeric protein consisting of an α chain and the heavy chain or light chain of an immunoglobulin and a chimeric protein consisting of a β chain and the heavy chain or light chain of an immunoglobulin simultaneously almost in the same amounts. This can be achieved by measuring the amounts of the chimeric protein consisting of an α chain and the heavy chain or light chain of an immunoglobulin and a chimeric protein consisting of a β chain and the heavy chain or light chain of an immunoglobulin produced in the cultured supernatant solution of the cell transfected by the recombinant vectors. For measurement, for example, the transfected cell can be cultured in a medium containing ^{35}S according to any publicly known method, for labeling

the proteins, and the amounts of the chimeric protein consisting of an α chain and the heavy chain or light chain of an immunoglobulin and a chimeric protein consisting of a β chain and the heavy chain or light chain of an immunoglobulin existing in the cultured supernatant solution can be estimated by immunoprecipitation using an anti-α chain antibody or an anti-β chain antibody respectively. As another method, the amounts of the chimeric protein consisting of an α chain and the heavy chain or light chain of an immunoglobulin and a chimeric protein consisting of a β chain and the heavy chain or light chain of an immunoglobulin existing in the cultured supernatant solution can be estimated according to the ELISA method using an anti-human immunoglobulin antibody and an anti-α chain antibody or an anti-β chain antibody. It is preferable to select a clone which produces almost the same large amounts of the chimeric proteins of the α and β chains in the cultured supernatant solution, for preparing an integrin-immunoglobulin chimeric protein heterodimer complex. The methods for labeling proteins, the methods of immunoprecipitation and the general methods of ELISA are described in a published book ("Antibody" Harlow, E., and Lane, D. (1988), Cold Spring Harbor Lab. Press, New York), but the methods are not limited to them. Any other method can also be used for detecting chimeric proteins.

Please replace the first full paragraph on page 21 with the following:

An integrin-immunoglobulin chimeric protein heterodimer complex can be purified by an established method using a protein A column chromatography by use of the nature of the immunoglobulin

portion. Furthermore, affinity chromatography using an antibody against the α or β chain can also be used. Moreover, the purification can also be achieved by affinity chromatography with a ligand bound to a carrier. General chromatographic methods can also be used in combination for the purification. If publicly known cases are applied in which integrin molecules are purified by these methods (Pytela, R. et al., Methods Enzymol., 144, 475-489 (1987), Santoro, S. A. et al., Biochem. Biophys. Res. Comm., 153, 217-223 (1988), Charo, I.F. et al., J. Cell Biol., 111, 2795-2800 (1990), Makarem, R. et al., J. Biol. Chem., 269, 4005-4011 (1994), Pfaff, M. et al., Eur. J. Immunol., 225, 975-984 (1994), Gulino, D. et al., Eur. J. Biochem., 227, 108-115 (1995), etc.), the purification of an integrin-immunoglobulin chimeric protein heterodimer complex can be achieved.

Please replace the paragraph bridging pages 35 and 36 with the following:

The template DNA, primers, dNTPs (an equimolar mixture of dATP, dCTP, dGTP and dTTT) and Taq polymeraze (Takara) were mixed in a PCR buffer (100 mM Tris-HCl, 500 mM KCl, 15 mM $MgCl^2$, 0.01% gelatin, pH 8.3), and in a thermal cycler (Perkin Elmer Cetus), the mixture was treated at 94°C for 1 minute for DNA denaturation, at 58 °C for 2 minutes for annealing the primers and at 72°C for 3 minutes for elongating the primers. This cycle of treatment was performed for 30 cycles. The amplified DNA was digested by restriction enzymes BamH I and Xba I, and the DNA fragment was purified by 1% agarose gel according to a general method ("Antibody", Harlow, E. and Lane, D. (1988), Cold Spring Harbor

Lab. Press, New York). It was linked, using a T4DNA ligase, with a large DNA fragment of pBluescriptSK(+) (STRATAGENE) purified and digested by restriction enzymes BamH I and Xba I. The plasmid DNA was used to transform Escherichia coli (JM109), and the transformant was selected, to obtain a plasmid DNA (IgG^1 Bluescript). Then, expression vector pcDL-SRα296 was digested by restriction enzyme BamH I, and blunted at the termini by T4DNA polymerase treatment, and a Not I linker was linked. The large DNA fragment obtained by digesting it by restriction enzymes Not I and Xho I and the small DNA fragment obtained by digesting IgG^1 Bluescript by restriction enzymes Not I and Xho I were purified according to a general method, and linked by T4DNA ligase. It was transformed into Escherichia coli (HB101) , and the transformant was selected, to obtain a plasmid DNA. Hereinafter this plasmid ($IgG_1SR\alpha$) is called the human IgG^1 expression vector. In the following examples, since the basic protocol of gene manipulation is the same as above, the description will be simplified.

Please replace the paragraph bridging pages 38 and 39 with the following:

The template cDNA, primers, dNTPs and Taq polymerase were mixed in a PCR buffer, and the mixture was treated by a thermal cycler at 94°C for 1 minute for DNA denaturation, at 58°C for 2 minutes for annealing the primers and at 72°C for 3 minutes for elongating the primers. This treatment was performed for 30 cycles. The amplified DNA fragments of α4-2 and α4-3 were digested by Pst I and EcoR I respectively, or EcoR I and BamH I and sub-cloned into pBluescriptKS(+) (STRATAGENE), to prepare plasmid DNAs

(hereinafter called α4-2 Bluescript and α4-3 Bluescript). Then, upstream of the α4-2 Bluescript, α4-1 was linked using Xba I and Stu I restriction sites, to prepare a plasmid DNA (hereinafter called α4-1-2 Bluescript).

Please replace the paragraph bridging pages 41 and 42 with the following:

Then, into the stabilized integrin β1·IgG heavy chain chimeric protein producing CHO cells, the integrin α4·IgG heavy chain chimeric protein expression vector was transfected according to the lipofectin method as described before. That is, integrin α4·IgGSRα and pSV2neo (BRL) were mixed at 10 : 1, and the mixture was mixed with lipofectin reagent. The mixture was added dropwise into the cells. After 18 hours of dropwise addition, the mixture was cultured in the said first selective medium for about 2 hours, and the cells were dispersed by trypsin-EDTA treatment. The cells were suspended in a second selective medium (nucleic acid-free αMEM medium (GIBCO BRL) containing 10% FBS (GIBCO) and 1 mg/ml neomycin (GIBCO)), and on a 96-well plate (CORNING), resistant cells were selectively cultured for about 10 days. The amount of integrin α4·IgG heavy chain chimeric protein and the amount of integrin β1·IgG heavy chain chimeric protein produced in the culture supernatant solution were determined according to the ELISA method (described later), and a clone which produced both the chimeric proteins in almost the same amounts was picked up. The clone was cloned twice according to the limiting dilution method, and stabilized as a clone capable of producing an α4·IgG heavy chain-β1·IgG heavy chain chimeric protein heterodimer complex.

Please replace the first full paragraph on page 48 with the following:

On the other hand, the immunoprecipitation pattern obtained by using the anti-integrin β1 antibody beads in the presence of 10 mM EDTA was the same as that in the presence of 1 mM $MgCl_2$, to clarify that the association between integrin α4•IgG heavy chain chimeric protein and integrin β1•IgG heavy chain chimeric protein does not depend on cations. The above results suggest that the eluted protein obtained in (3) of Example 6 was certainly an α4•IgG heavy chain-β1•IgG heavy chain chimeric protein heterodimer complex, and if the result of (4) of Example 6 is also taken into account, it is strongly suggested that the association between both the proteins is a stable association through a disulfide bond existing in the IgG heavy chains.

Please replace the heading on page 48 with the following:

(2) Examination of the structural stability of α4·IgG heavy chain-β1·IgG heavy chain chimeric protein heterodimer complex by sequential immunoprecipitation.